REMARKS

Reconsideration and withdrawal of the rejections of this application are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. STATUS OF CLAIMS

Claims 1, 3-8, 13-15, and 18-22 were pending in the application. Claims 1, 3, 5, 13-15, and 18-22 have been cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Applicant reserves the right to pursue the subject matter of the cancelled claims in this or future applications. Claim 4 has been amended. Support for the amended claim can be found throughout the specification and claims as originally filed. See, e.g., the abstract and paragraphs 0015, 0016, and 0024 of the published application. No new matter has been introduced.

The issues raised by the Examiner in the Office Action are addressed below in the order they appear in the prior Action.

II. THE REJECTIONS UNDER 35 U.S.C. § 103 ARE OVERCOME

Claims 1, 3-8, 13-15, and 18-22 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Barrowcliffe et al. (1981, Thromb. Res. Vol. 21, page 181; "Barrowcliffe") in view of Lang et al. (U.S. Patent No. 5,506,112; "Lang") taken with Capon et al. (U.S. Patent No. 4,965,199; "Capon"). Applicant respectfully traverses.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Although a teaching, suggestion, or motivation to combine is no longer rigidly required for a finding of obviousness, it remains the primary guarantor against a non-statutory hindsight analysis. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the § 103 rejection to be proper, both the

suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicant's disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Furthermore, the Supreme Court reaffirmed the factors set out in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18: "[T]he scope and content of the prior art are determined; differences between the prior art and the claims at issue are...ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727.

Applying the law to the instant facts, the references relied upon by the Office Action do not disclose, suggest or enable Applicant's invention. None of the cited references, alone or in combination, teach or suggest the invention recited in the pending claims.

The cited references do not teach or suggest actually administering FVIII together with FIXa to a subject for the treatment of hemophilia. Further, in view of the claims as amended, the cited art does not teach or suggest administering such a composition to a subject lacking anti-FVIII antibodies.

Barrowcliffe notes that "about 15 % of haemophiliac patients develop antibodies to FVIII and their treatment poses a major difficulty" (page 34). Barrowcliffe relates to the addition of purified FIXa and phospholipid for the protection of FVIII from subsequent inactivation by antibody. However, the major protective effect was provided by phospholipid (see paragraph bridging pages 34 and 35). Barrowcliffe also notes that "the addition of phospholipid to FVIII concentrates could have important clinical applications in the treatment of haemophiliacs with antibodies to FVIII" (page 34, last sentence of the abstract).

Barrowcliffe thus pertains to the protective effect of **phospholipid** on FVIII, and does not teach or suggest treating hemophiliac patients **that do not present with anti-FVIII antibodies**. As such, Barrowcliffe does not teach or suggest the administration of FIXa and FVIII to a subject, and in particular, does not teach or suggest administering such a combination to a hemophiliac patient that does not present with anti-FVIII antibodies.

The invention recited in the pending claims is based on the surprising finding that FIXa allows the concentration of FVIII in a composition for treating hemophilia to be reduced (see, for

example, page 3, lines 6-10 of the application as originally filed). This is based on the demonstration that the FIXa concentration is very important in determining the clotting process, especially at low FVIII concentrations. This is clearly shown by Figure 3A, discussed at page 6, lines 15-22; page 28, line 31 to page 29, line 7; and page 31, lines 4-7 of the application as originally filed.

As can be seen from Figure 3A, even in normal plasma (diamond markers), there was a slight shift in the clotting curve between high and low FIXa concentrations. However, in the hemophiliac plasma (lacking FVIII, asterisk markers), there is a dramatic difference in clotting depending on FIXa concentration. As mentioned at the top of page 29, at low concentrations of FIXa, virtually no thrombin was generated. As summarized on page 31, this shows that FIXa concentration is particularly important in generating thrombin at low FVIII concentrations. Thus, the invention recited in the pending claims involving the addition of FIXa allows lower amounts of FVIII to be used (see, for example, page 5, lines 10-13). The invention recited in the pending claims therefore provides an improved treatment of hemophilia in subjects that do not have anti-FVIII antibodies, involving the use of a lower concentration of FVIII.

Furthermore, Barrowcliffe is entirely concerned with hemophilia in which FVIII antibodies reduce the activity of FVIII. There is no suggestion in Barrowcliffe that would lead one of ordinary skill in the art to administer FIXa in combination with FVIII to a subject that **does not present with anti-FVIII antibodies**. Even assuming Barrowcliffe pertains to an advantageous effect of FIXa in protecting FVIII from antibodies, one of ordinary skill in the art would have derived no suggestion to administer FIXa with FVIII to a subject **without** anti-FVIII antibodies. One of ordinary skill in the art would not have expected any useful effect to be achieved by including FVIII in such circumstances. Thus, based on Barrowcliffe, it would not have been obvious to the ordinarily skilled artisan to administer these two agents together in a composition as recited in the pending claims.

Lang and Capon fail to remedy the deficiencies of Barrowcliffe. Further to the arguments of record, Lang relates only to *in vitro* assays, using a composition comprising a low concentration of factor IXa and other components. This composition is added to a sample to measure factor VIII activity. There is no suggestion whatsoever in Lang that a composition comprising FVIII and FIXa should be used in a therapeutic method to treat a hemophiliac patient lacking anti-FVIII antibodies.

Capon does not teach or suggest a method of treating hemophilia A or hemophilia B, comprising administering to a patient in need thereof a pharmaceutical composition consisting essentially of coagulation factor VIII and IXa. Further to the arguments of record, there is no teaching or suggestion in Capon that factor IXa should actually be added to a composition to be used therapeutically. Moreover, there is no suggestion in Capon that such a composition should be used to treat a hemophiliac patient that does not have anti-FVIII antibodies. Capon merely relates to factor IXa as part of the blood clotting cascade (see Figure 1), and therefore, factor IXa and the other factors shown would normally already be present in an individual. There would therefore be no motivation to add factor IXa to a composition comprising factor FVIII for treating hemophilia, let alone a subject that does not have anti-FVIII antibodies.

In view of the foregoing, the cited references do not render the pending claims *prima facie* obvious. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully requested.